FDA Presentation
March 27, 2014
Molecular and Clinical Genetics Advisory Committee Panel Meeting

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Exact Sciences Corp.

Cologuard™

PMA P130017

Cologuard Review Team

• Nina Hunter, Ph.D.	Lead Reviewer
• Abraham Tzou, M.D.	Medical Officer
• Kyunghee Song, Ph.D.	Statistics
• Qin Li, Ph.D.	Statistics
• Gene Pennello, Ph.D.	Statistical Team Leader
• Cheng Zhang, Ph.D.	Software
• Kennita Riddick, M.S.	Manufacturing
• Tamika Allen, R.N., B.S.N., M.S.	Bioresearch Monitoring
• Eunice Lee, Ph.D.	Analytical
• Joshua Levin, Ph.D.	Analytical
• Hong Cheng, Ph.D.	Epidemiology
• David Windt, M.S.	Labeling
• Elizabeth Hillebrenner, M.S.	CMS Liaison

Rationale for Meeting

To obtain Panel input on:

- Safety and effectiveness of *Cologuard*
- Whether the benefits outweigh the risks of using *Cologuard* for the proposed intended use

FDA Presentation Part I

- Regulatory History
- Proposed Indications for Use and Contraindications
- Device Overview and Workflow
- Summary of Analytical Studies
- Introduction to Clinical Study Design

FDA Presentation Part II

- Patient Accountability
- Primary and Secondary Effectiveness Results
- Secondary Objectives
- Predictive Values
- Statistical Analyses:
  - Intent to Diagnose
  - Age-Adjusted Sensitivity and Specificity
  - Receiver Operating Characteristics (ROC)
  - Benefit-Risk
  - Subgroup

FDA Presentation Part III

- Key aspects of clinical studies
- FDA questions for Panel Discussion
- Proposed post approval study
- Additional review and labeling considerations

Regulatory History

- Modular Pre-Market Application (PMA)
  - First module December 2012
  - PMA complete July 2013 → P130017
  - Priority review
  - Deficiency letter issued September 2013
  - Sponsor response to deficiencies January 2014
- Pilot submission for Center for Medicare and Medicaid Services (CMS) Parallel Review Program

Proposed Indications for Use

Cologuard is intended for use as an adjunctive screening test for the detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer or pre-malignant colorectal neoplasia. *Cologuard* is not intended as a replacement for diagnostic colonoscopy. A positive result in *Cologuard*, as with any screening test, should be followed by colonoscopy. *Cologuard* is intended for patients who are typical candidates for colorectal cancer screening: adults of either sex, 50 years or older, who are at average risk for colorectal cancer.

Proposed Contraindications

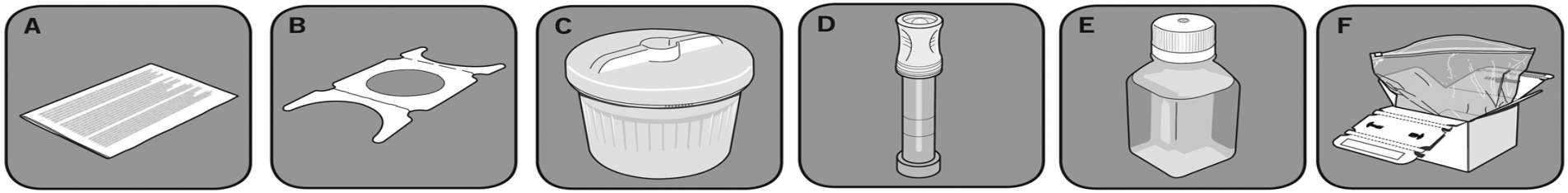
Cologuard is not suitable for everyone. This test is indicated for men and women, age 50 years or older, who are at average risk for development of colorectal cancer.

Patients should inform their doctor:

- Colorectal cancer, adenomas, or other related cancers
- Positive result from another colorectal cancer screening method (last 6 months)
- Diagnosed with a high-risk condition for colorectal cancer
- Diagnosed with a relevant hereditary cancer syndrome

Device Overview and Workflow

- Exact Sciences Stool Collection Kit

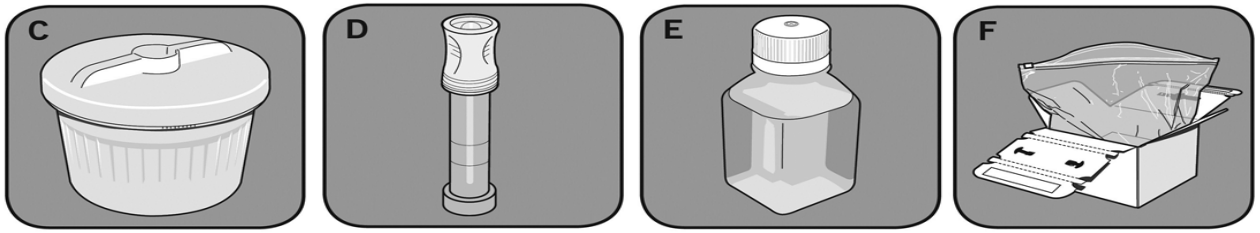


instructions for use | bracket | stool collection container | protein sample tube | preservative | shipping box

- Assay: series of reagents, controls, laboratory equipment/instruments, and software

Note: cartoons provided by Exact Sciences

Device Overview and Workflow



stool collection container

protein sample tube

preservative

shipping box

Device Overview and Workflow

DNA Capture

Bisulfite Conversion

KRAS Cleanup

QuARTS™ Assay

Test Result: positive or negative

ELISA-based Hemoglobin Assay (FIT)

Device Overview and Workflow

3 independent families of markers

DNA Capture

Bisulfite Conversion

NDRG4

BMP3

KRAS Cleanup

KRAS

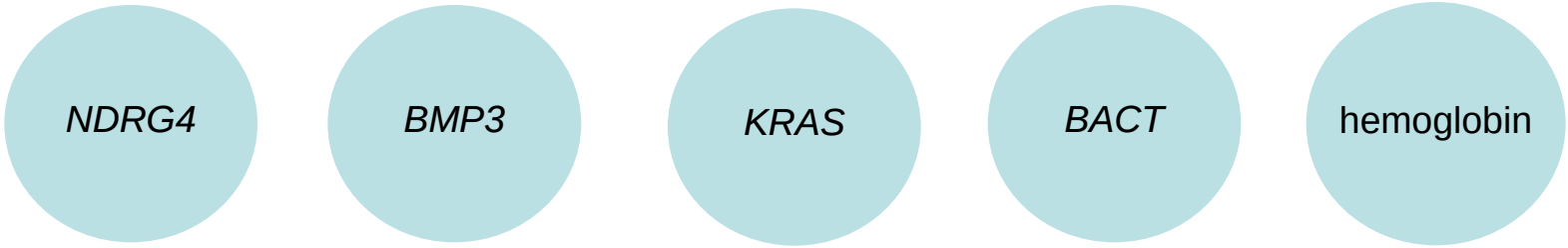
QuARTS™ Assay

Test Result

ELISA-based Hemoglobin Assay (FIT)

Summary of Analytical Studies

Analytes for Analytical Studies



Summary of Analytical Studies

- Analytical Sensitivity
  - Limit of Detection
  - Limit of Quantitation
  - Limit of Blank
  - Linear Range, Linearity
- Analytical Specificity
  - Double KRAS mutation
  - Partially Methylated Targets
  - WT KRAS
  - Cross-Reactivity
- Interfering Substances, Carry-Over, and Cross Contamination
- Development and Validation of the *Cologuard* Algorithm and Cut-Off
- Precision and Reproducibility (lab-to-lab and lot-to-lot)
- Robustness
- Serial Stool Study
- Analytical Specificity to Other Cancers
- Shelf-Life and Packaging Testing

Clinical Study Design of DeeP-C

- Prospective enrollment (age 50-84*)
- 90 sites: 89 in US, one in Canada
- 12,776 patients enrolled
- Enrollment weighted toward ages 65-84 (64%)
- Cross-sectional study design
- Subject underwent colonoscopy within 90 days of sample collection
- Head-to-head FIT analysis (PolyMedco)
- Stool samples collected for analysis at three testing sites
- Blinding: Evaluators of *Cologuard*, FIT, biopsy histology mutually masked to the other results

*one 44-year old and two 49-year olds were included in study; no significant impact on performance

Six Histopathological Categories

Note: Category 1= CRC; Category 2 = AA; & Category 3 to 6

Category	Findings
1	CRC, all stages (I-IV)
2	Advance adenoma, including the following subcategories: 2.1 – Adenoma with carcinoma *in situ*/high grade dyplasia, any size 2.2 – Adenoma, villous growth pattern (≥25%), any size 2.3 – Adenoma ≥1.0 cm in size, or 2.4 – Serrated lesion, ≥1.0 cm in size
3	1 or 2 adenoma(s), >5 mm in size, or <10 mm size, non-advanced
4	≥3 adenomas, <10mm, non-advanced
5	1 or 2 adenoma(s), ≤5 mm in size, non-advanced
6	Negative – No neoplastic findings 6.1 – negative upon histopathological review 6.2 – no findings on colonoscopy; no histopathological review

DeeP-C Inclusion Criteria

- Patient is average risk for development of colorectal cancer
- Patient is 50 to 84 years of age inclusive
- Patient has not had a colonoscopy in the previous 9 years

DeeP-C Exclusion Criteria

- No condition that in the opinion of the investigator that should preclude participation in the study
- No history of CRC or AA or aerodigestive tract cancer
- No prior colorectal resection for any reason other than sigmoid diverticular disease
- No overt rectal bleeding within the previous 30 days
- No diagnosis or personal history of high-risk conditions for colorectal cancer
- Family history

DeeP-C Study Objectives

Primary objectives

- *Cologuard* sensitivity for CRC has 95% lower confidence bound ≥ 65% (one-sided)

Six Histopathological Categories

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DeeP-C Study Objectives

Primary objectives

- *Cologuard* sensitivity for CRC has 95% lower confidence bound ≥ 65% (one-sided)
- *Cologuard* specificity for categories 3-6 has 95% lower confidence bound ≥ 85% (one-sided)

Six Histopathological Categories

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DeeP-C Study Objectives

Primary objectives

- *Cologuard* sensitivity for CRC has 95% lower confidence bound ≥65% (one-sided)
- *Cologuard* specificity for categories 3-6 has 95% lower confidence bound ≥85% (one-sided)

Secondary objectives

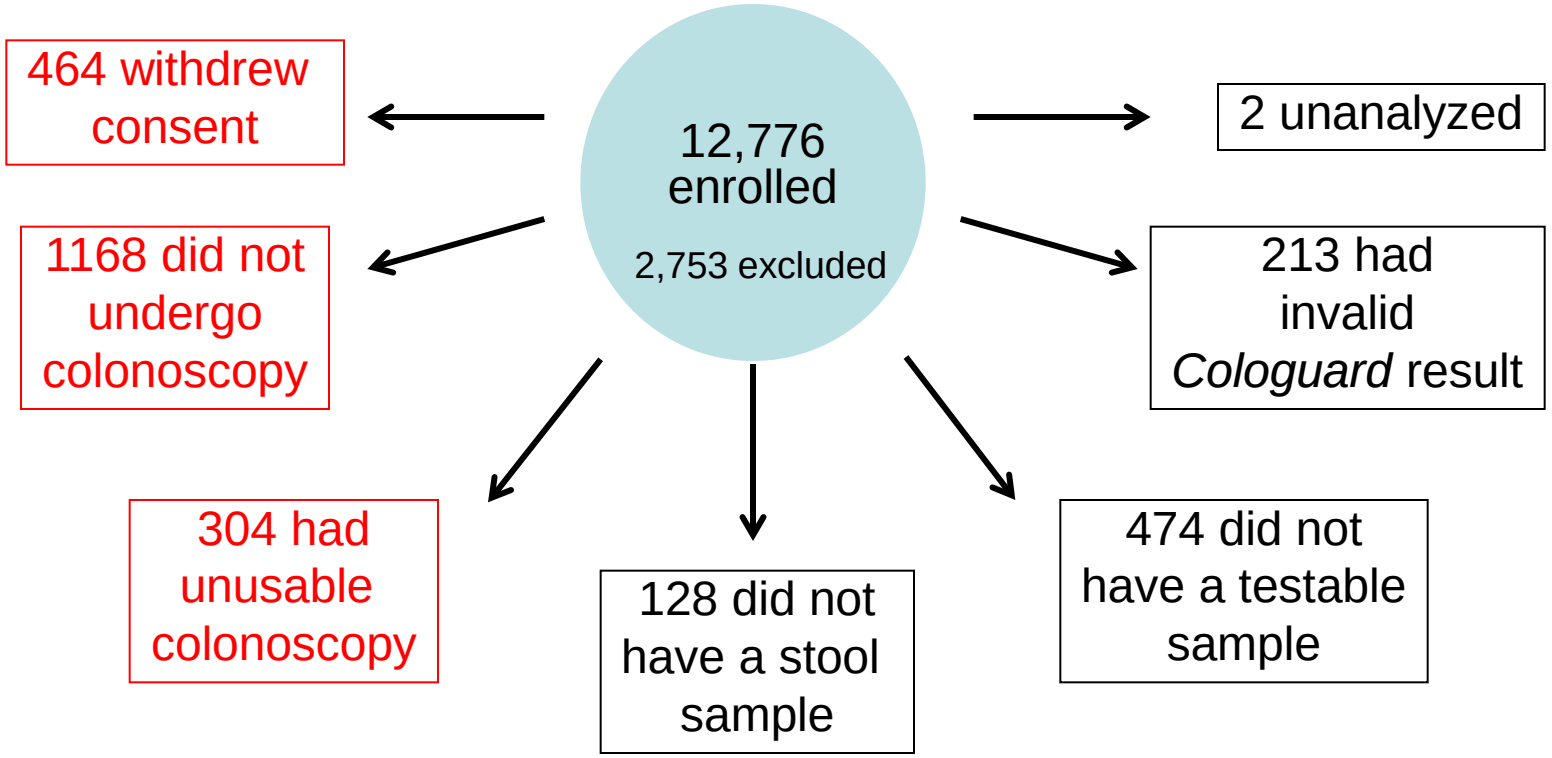
- *Cologuard* is noninferior to FIT* for CRC sensitivity (with respect to 5% noninferiority margin)
- *Cologuard* is superior to FIT* for AA sensitivity

*Note: PolyMedco FIT

FDA Presentation Part II

- Patient Accountability
- Primary and Secondary Effectiveness Results
- Classification of CRC, AN
- Predictive Values
- Statistical Analyses:
  - Intent to Diagnose
  - Age-Adjusted Sensitivity and Specificity
  - Receiver Operating Characteristics (ROC)
  - Benefit-Risk
  - Subgroup

DeeP-C Patient Accountability



No clinical information

With clinical information, without *Cologuard* result

DeeP-C Study Populations

- 12,776 patients enrolled
- 2,753 excluded (for reasons on last slide)
- Primary effectiveness population
  - Available *Cologuard* and histology results
  - 10,023 (12,776 – 2,753) patients
- Secondary effectiveness population
  - Available *Cologuard*, PolyMedco FIT, and histopathology results
  - 9,989 patients

Six Histopathological Categories

Category 1= CRC; Category 2 = AA;

Categories 1 & 2 = AN; Categories 3 to 6 = non-AN

Category	Findings
1	CRC, all stages (I-IV)
2	Advance adenoma, including the following subcategories: 2.1 – Adenoma with carcinoma *in situ*/high grade dyplasia, any size 2.2 – Adenoma, villous growth pattern (≥25%), any size 2.3 – Adenoma ≥1.0 cm in size, or 2.4 – Serrated lesion, ≥1.0 cm in size
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5	1 or 2 adenoma(s), ≤5 mm in size, non-advanced
6	Negative – No neoplastic findings 6.1 – negative upon histopathological review 6.2 – no findings on colonoscopy; no histopathological review

Classification Performance of a Test

CRC Sensitivity†	Proportion of patients in histological category 1 (CRC) who test positive
CRC Specificity	Proportion of patients in histological categories 2-6 who test negative

Classification Performance of a Test

CRC Sensitivity†	Proportion of patients in histological category 1 (CRC) who test positive
CRC Specificity	Proportion of patients in histological categories 2-6 who test negative
AN Sensitivity	Proportion of patients in histological categories 1-2 (CRC, AA) who test positive
AN Specificity†	Proportion of patients in histological categories 3-6 who test negative

† The primary performance measures

Classification Performance of a Test

CRC Sensitivity†	Proportion of patients in histological category 1 (CRC) who test positive
CRC Specificity	Proportion of patients in histological categories 2-6 who test negative
AN Sensitivity	Proportion of patients in histological categories 1-2 (CRC, AA) who test positive
AN Specificity†	Proportion of patients in histological categories 3-6 who test negative
AA Sensitivity††	Proportion of patients in histological category 2 (AA) who test positive

† The primary performance measures

††A secondary performance measure

Evidence for Primary Objectives

- **Primary Objectives.** *One-sided* 95% lower confidence bound (LB)
  - ≥ 65% for CRC sensitivity
  - ≥ 85% for AN specificity
- **Other Submissions.** *Two-sided* 95% confidence interval (CI) is compared against the study goal
- The two-sided 95% CI is a higher level evidence for a study goal and will be presented here as well

Primary Effectiveness Results

Cologuard (CG) result by Histopathology

CG	CRC Cat. 1	AA Cat. 2	Non-AN Cat. 3-6
−	5 (7.7)	438 (57.6)	7967 (86.6)
+	60 (92.3)	322 (42.4)	1231 (13.4)

Secondary Effectiveness Results

CG by FIT, Stratified by Histopathology

CRC, Cat. 1		
	FIT	
CG	**–**	**+**
–	4	1
+	13	47

AA, Cat. 2		
	FIT	
CG	**–**	**+**
–	407	29
+	170	151

Non-AN, Cat. 3-6		
	FIT	
CG	**–**	**+**
–	7787	149
+	908	323

Pre-specified Analyses

Primary and Secondary
Study Goals

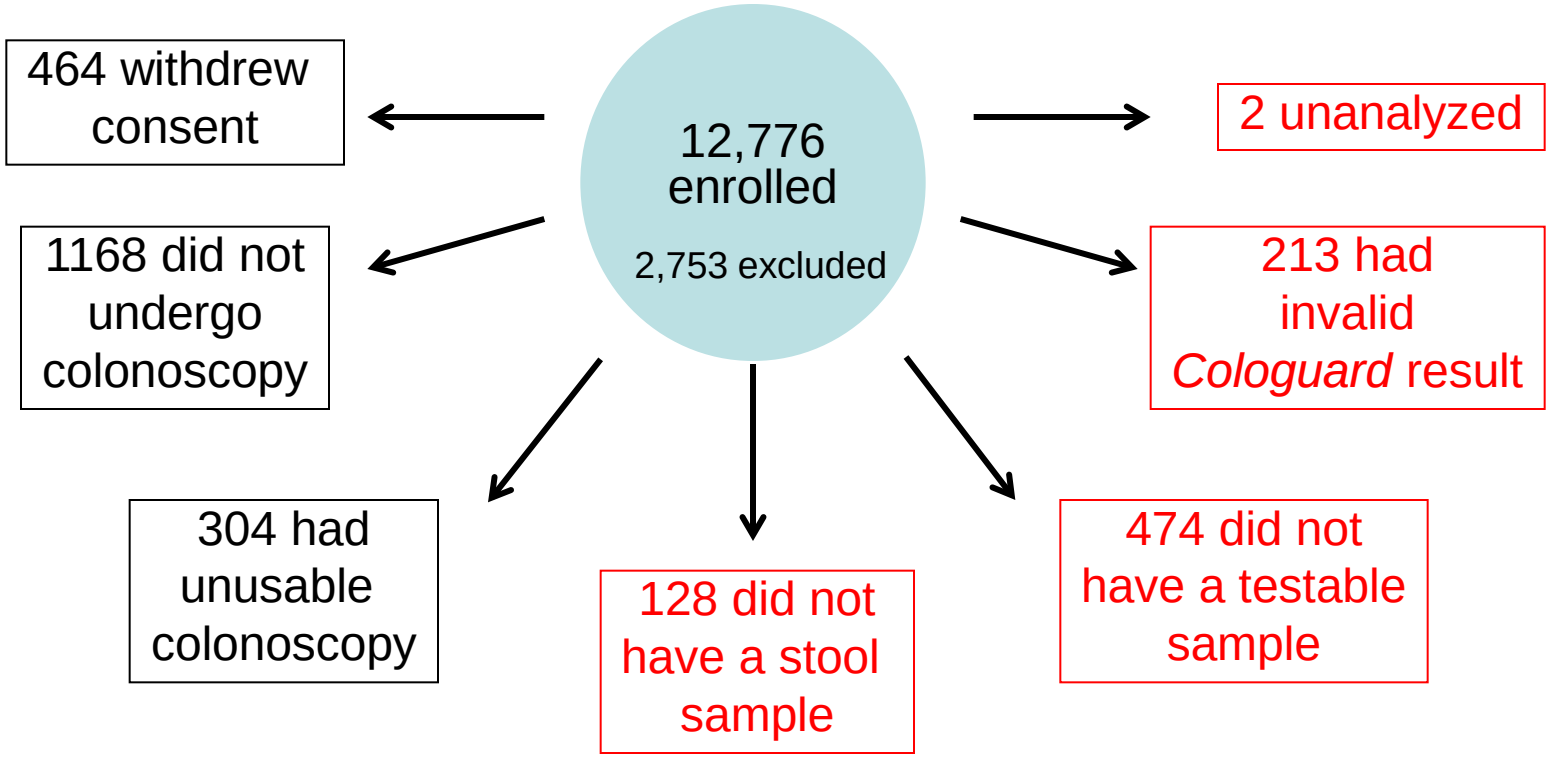
Primary Study Goals

- **CRC sensitivity** ≥ 65% (1-sided 95% CI LB)
  - CRC Sensitivity was 92.3% (60/65)
  - 1-sided 95% lower confidence bound was 84.5%
    Study goal of ≥ 65% was met
- **AN specificity** ≥ 85% (1-sided 95% CI LB)
  - AN Specificity was 86.6% (7967/9198)
  - 1-sided 95% lower confidence bound was 86.0%
    Study goal of ≥ 85% was met

Intent-to-Diagnose (ITD) Analysis (FDA)

- 12,776 enrolled
  - 10,023 with *Cologuard* and histology
  - 817 with missing *Cologuard* results
  - 10,840 (10,023+817) in ITD analysis

DeeP-C Patient Accountability



No clinical information

With clinical information, without *Cologuard* result

Primary Study Goals, ITD Analysis

- **CRC sensitivity** ≥ 65% (1-sided 95% CI LB)
  - CRC Sensitivity was 92.3%
  - 1-sided 95% lower confidence bound was 84.5%
    Study goal of ≥ 65% was met
  - 2-sided 95% CI was 83.0-97.5% (FDA)
    Study goal of ≥ 65% was met with 2-sided 95% CI
- **AN specificity** ≥ 85% (1-sided 95% CI LB)
  - AN Specificity was 86.6%
  - 1-sided 95% lower confidence bound was 86.0%
    Study goal of ≥ 85% was met
  - 2-sided 95% CI was 85.9-87.3% (FDA)
    Study goal of ≥ 85% was met with 2-sided 95% CI

Secondary Study Goal

- **CRC Sensitivity**

  Goal: *Cologuard* is **non-inferior** to FIT (5% margin)

  - 92.3% (60/65) for *Cologuard*
  - 73.9% (48/65) for FIT
  - Difference = 18.4%; 95% CI 5.9-31.5% > 0% > – 5%

  Conclusion: *Cologuard* **non-inferior** to FIT (goal was met)

	FIT	
CG	**–**	**+**
–	4	1
+	13	47

Secondary Study Goal

- **CRC Sensitivity**

  Goal: *Cologuard* is **non-inferior** to FIT (5% margin)

  - 92.3% (60/65) for *Cologuard*
  - 73.9% (48/65) for FIT
  - Difference = 18.4%; 95% CI 5.9-31.5% > 0% > – 5%

  Conclusion: *Cologuard* **superior** to FIT

	FIT	
CG	**–**	**+**
–	4	1
+	13	47

Secondary Study Goal

- **AA Sensitivity**

  Goal: *Cologuard* is **superior** to FIT

  - 42.4% (321/757) for *Cologuard*
  - 23.8% (180/757) for FIT
  - Difference = 18.6%; 95% CI 15.3-22.1% is > 0%

  Conclusion: *Cologuard* was **superior** to FIT (goal was met)

	FIT	
CG	**–**	**+**
–	407	29
+	170	151

CRC Classification

Primary Effectiveness Population

Cologuard Performance, CRC (FDA)

- **CRC sensitivity** ≥ 65% (2-sided 95% CI LB)
  - CRC Sensitivity was 92.3% (60/65)
  - 2-sided 95% CI 83.0-97.5%
    Study goal of ≥ 65% was met
- **CRC specificity** ≥ 85% (2-sided 95% CI LB)
  - CRC Specificity was 84.4% (8405/9958)
  - 2-sided 95% CI 83.7-85.1%
    Study goal of ≥ 85% was not met

CRC sensitivity, CRC specificity, weighted to 2010 US census age distribution (FDA analysis)

Age	US %†	Study %
50-59	44.56	28.7
60-64	18.71	8.2
65-69	13.05	36.7
70-74	9.93	17.3
75-79	7.61	6.8
80-84	6.14	2.2

CRC sensitivity, CRC specificity, weighted to 2010 US census age distribution (FDA analysis)

Age	US %†	Study %	CRC SE	CRC SP
50-59	44.56	28.7	100.0	90.4
60-64	18.71	8.2	75.0	86.9
65-69	13.05	36.7	95.0	83.4
70-74	9.93	17.3	88.9	80.0
75-79	7.61	6.8	100.0	75.5
80-84	6.14	2.2	90.0	76.2
Observed			92.3 83.0-97.5	84.4 83.7-85.1
Weighted to US			90.9 79.3-97.6	85.8 85.0-86.6

Age-adjusted Complementary CRC SE, CRC SP Analysis:

CRC SE 90.9%, 2-sided 95% CI 79.3-97.6%. ≥65% goal was met

CRC SP 85.8%, 2-sided 95% CI 85.0-86.6%. ≥85% goal was met

AN Classification

Primary Effectiveness Population

Cologuard Performance, AN (FDA)

- **AN sensitivity** ≥ 65% (2-sided 95% CI LB)
  - AN Sensitivity was 46.3% (382/825)
  - 2-sided 95% CI 42.9-49.8%
    Study goal of ≥ 65% was not met
- **AN specificity** ≥ 85% (2-sided 95% CI LB)
  - AN Specificity was 86.6% (7967/9198)
  - 2-sided 95% CI, 85.9-87.3%
    Study goal of ≥ 85% was met

AN is colorectal cancer and/or advanced adenoma

AN sensitivity, AN specificity, weighted to 2010 US census age distribution (FDA analysis)

Age	US %†	Study %	AN SE	AN SP
50-59	44.56	28.7	40.5	92.2
60-64	18.71	8.2	44.3	89.0
65-69	13.05	36.7	44.9	85.7
70-74	9.93	17.3	51.2	82.5
75-79	7.61	6.8	51.5	77.8
80-84	6.14	2.2	64.0	77.9
Observed			46.3 42.9-49.8	86.6 85.9-87.3
Weighted to US			46.4 42.3-50.4	87.9 87.1-88.7

Age-adjusted Complementary AN SE, AN SP Analysis:

AN SE 46.4%, 2-sided 95% CI 42.3-50.4%. ≥ 65% goal was not met

AN SP 87.9%, 2-sided 95% CI 87.1-88.7%. ≥ 85% goal was met

Predictive Value

(FDA Analysis)

Predictive Values, %, 95%CI (Count)

CG	CRC, Cat. 1	AA, Cat. 2	Non-AN, Cat. 3-6	N
–	0.06, 0.02-0.14 (5)	5.2, 4.7- 5.7 (438)	94.7, 94.2-95.2 (7967)	8410
+	3.72, 2.85-4.76 (60)	20.0,18.0-22.0 (322)	76.3, 74.2-78.4 (1231)	1613
Pre-test	0.65, 0.50-0.83 (65)	7.6, 7.1- 8.1 (760)	91.8, 91.2-92.3 (9198)	10023

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Pre-test	0.65, 0.50-0.83 (65)	7.6, 7.1- 8.1 (760)	91.8, 91.2-92.3 (9198)	10023

CRC: PPV 3.72% is 5.7 times > than CRC prevalence 0.65%

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CRC: PPV 3.72% is 5.7 times > than CRC prevalence 0.65%

AA: PPV 20.0% is 2.6 times > than AA prevalence 7.6%

Predictive Values, %, 95%CI (Count)

CG	CRC, Cat. 1	AA, Cat. 2	Non-AN, Cat. 3-6	N
−	0.06, 0.02-0.14 (5)	5.2, 4.7- 5.7 (438)	94.7, 94.2-95.2 (7967)	8410
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CRC: PPV 3.72% is 5.7 times > than CRC prevalence 0.65%

AA: PPV 20.0% is 2.6 times > than AA prevalence 7.6%

non AN: Prevalence of AN (CRC, AA) = 100 – 91.8 = 8.2% is 1.6 times > than 100(1 – NPV) = 5.3%

Predictive Values, %, 95%CI (Count)

Cologuard

CG	CRC, Cat. 1	AA, Cat. 2	Non-AN, Cat. 3-6	N
−	0.06, 0.02-0.14 (5)	5.2, 4.7 - 5.7 (436)	94.7, 94.2-95.2 (7936)	8377
+	3.72, 2.85-4.77 (60)	20.0,18.0-22.0 (321)	76.4, 74.2-78.4 (1231)	1612

PolyMedco FIT

Poly FIT	CRC, Cat. 1	AA, Cat. 2	Non-AN, Cat. 3-6	N
−	0.18, 0.11-0.29 (17)	6.2, 5.7 - 6.7 (577)	93.6, 93.0-94.1 (8695)	9289
+	6.86, 5.10-8.99 (48)	25.7, 22.5-29.1 (180)	67.4, 63.8-70.9 (472)	700

Pre-test	0.65, 0.50-0.83 (65)	7.6, 7.1- 8.1 (757)	91.8, 91.2-92.3 (9167)	9989

CRC PPV < for *Cologuard* (3.72%) than FIT (6.86%)

Predictive Values, %, 95%CI (Count)

Cologuard

CG	CRC, Cat. 1	AA, Cat. 2	Non-AN, Cat. 3-6	N
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Pre-test	0.65, 0.50-0.83 (65)	7.6, 7.1- 8.1 (757)	91.8, 91.2-92.3 (9167)	9989

AA PPV < for *Cologuard* (20%) than FIT (25.7%)

Predictive Values, %, 95%CI (Count)

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+	6.86, 5.10-8.99 (48)	25.7, 22.5-29.1 (180)	67.4, 63.8-70.9 (472)	700

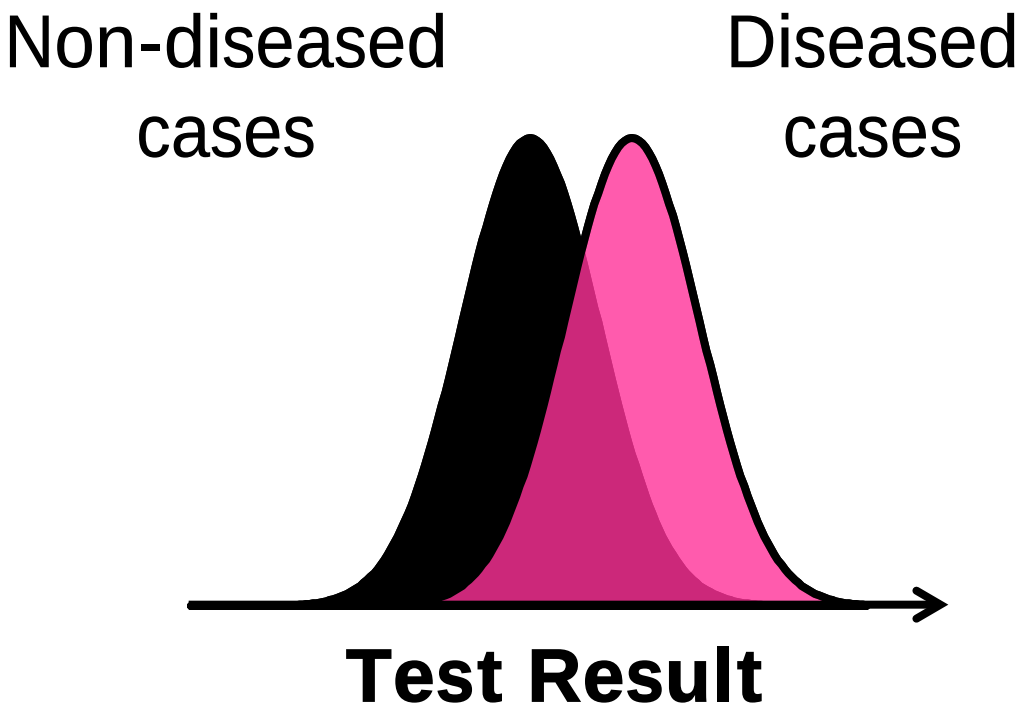
Pre-test	0.65, 0.50-0.83 (65)	7.6, 7.1- 8.1 (757)	91.8, 91.2-92.3 (9167)	9989

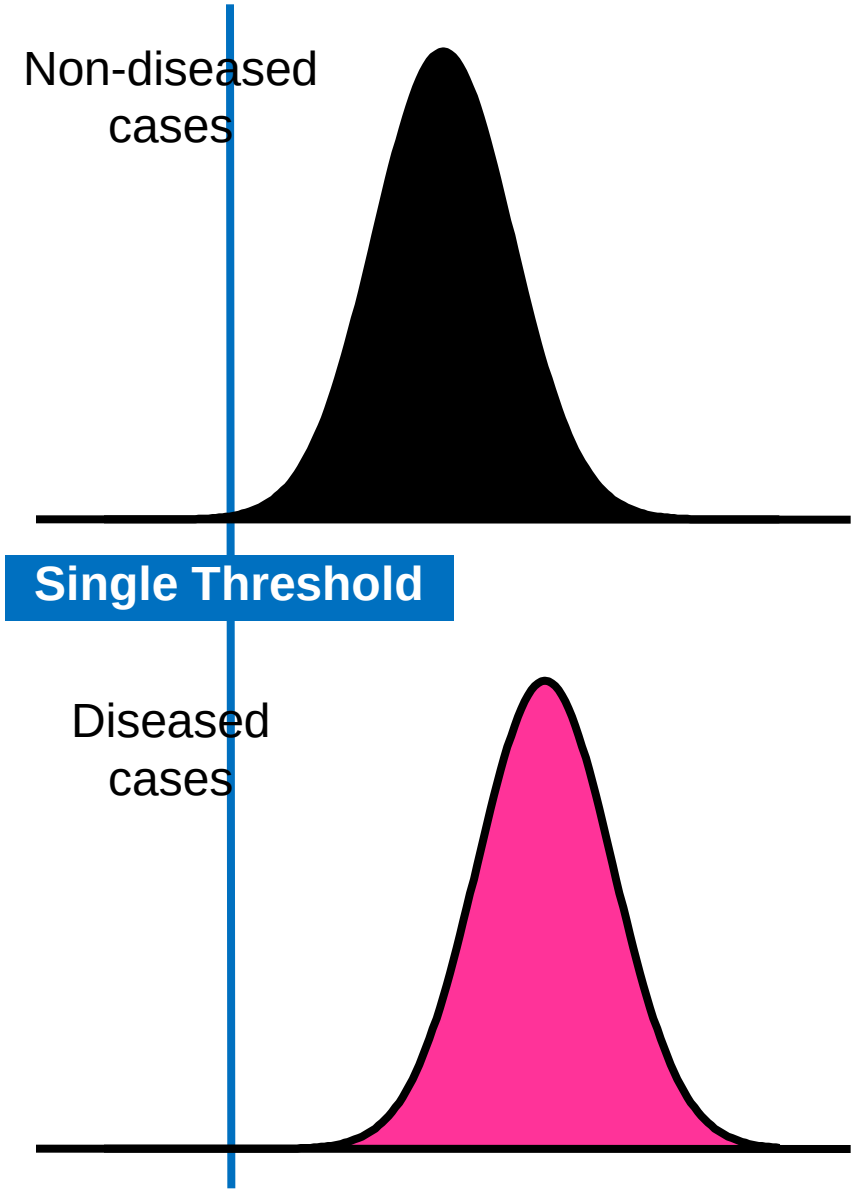
AN NPV> for *Cologuard* (94.7%) than FIT (93.6%)

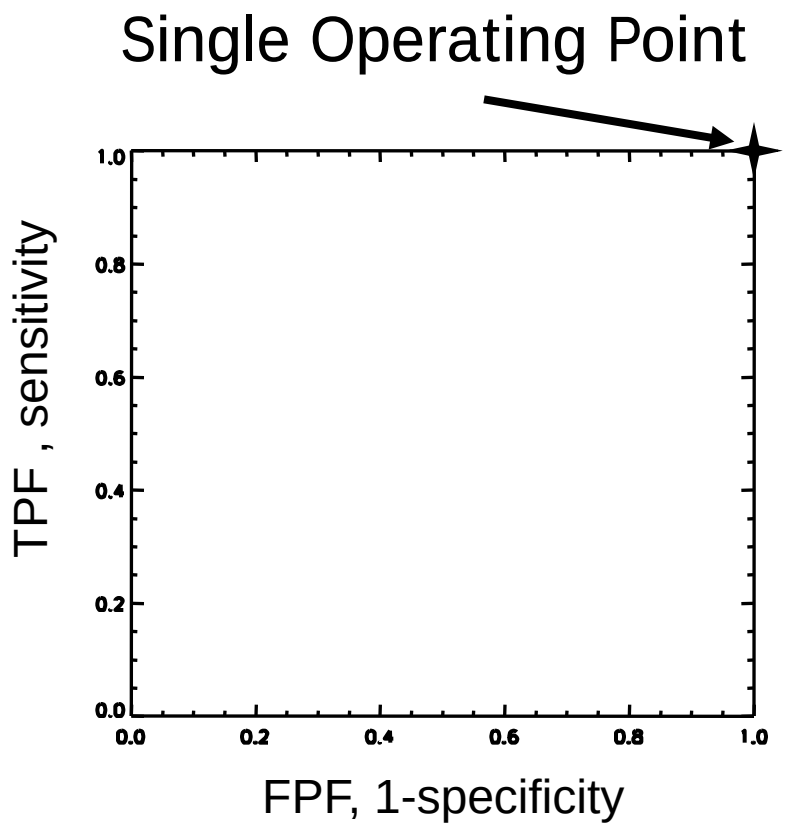
ROC Analysis, CRC

Secondary Effectiveness Population

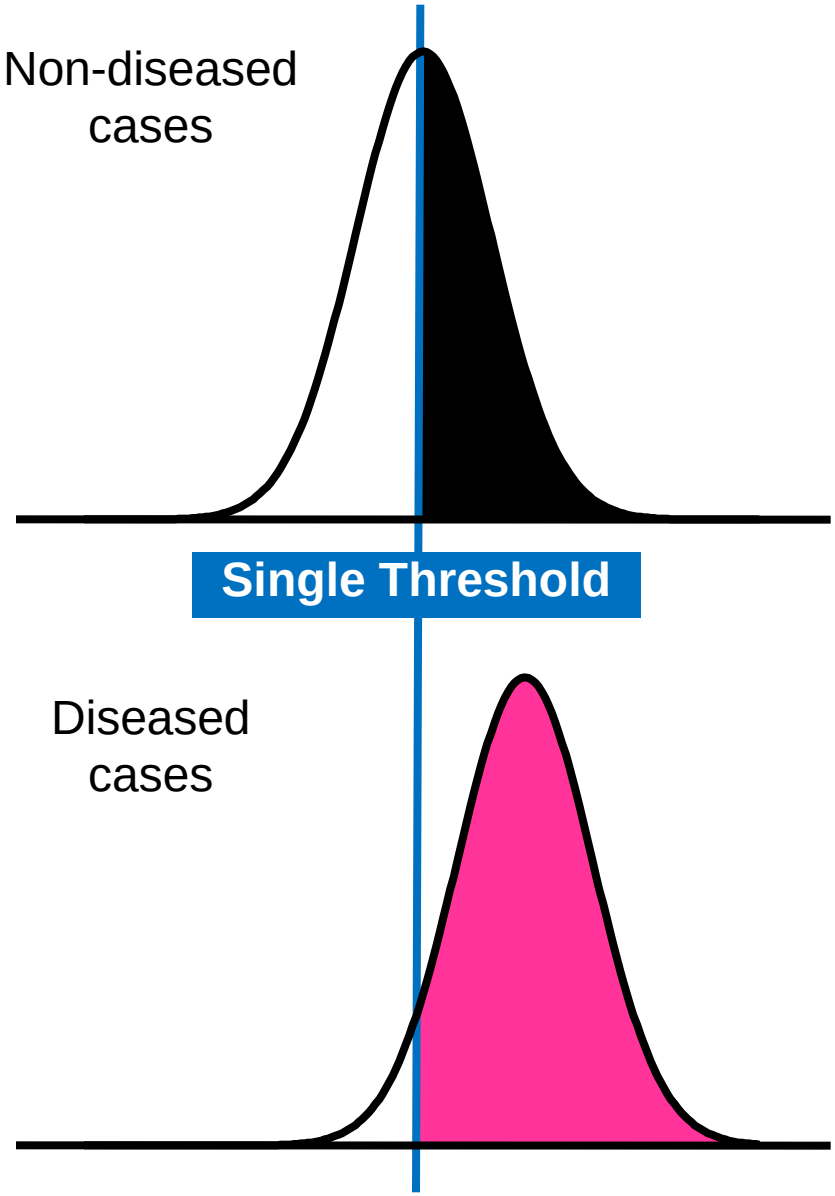
ROC Analysis

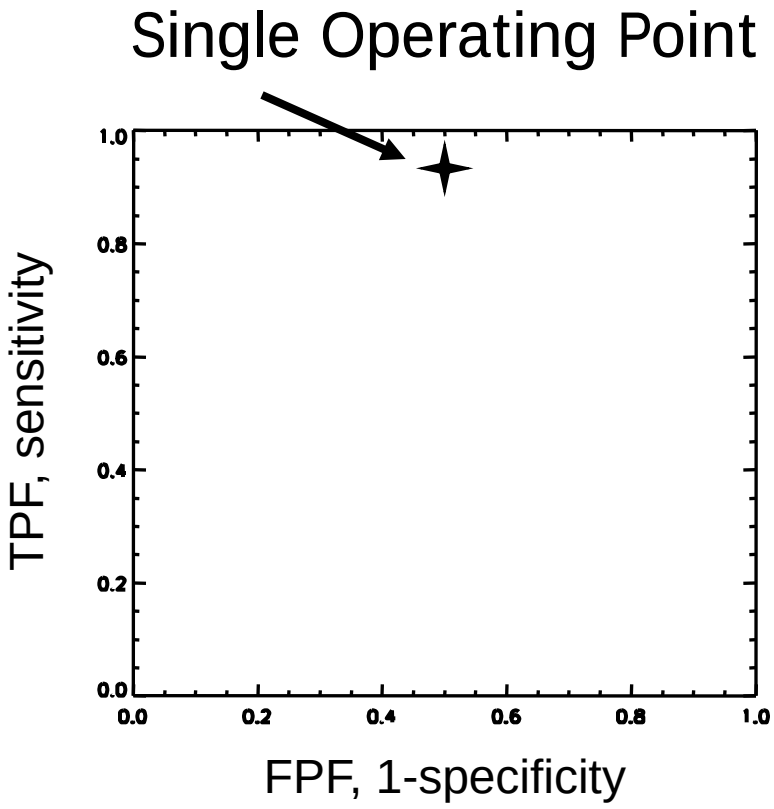






TPF=true positive fraction
FPF=false negative fraction





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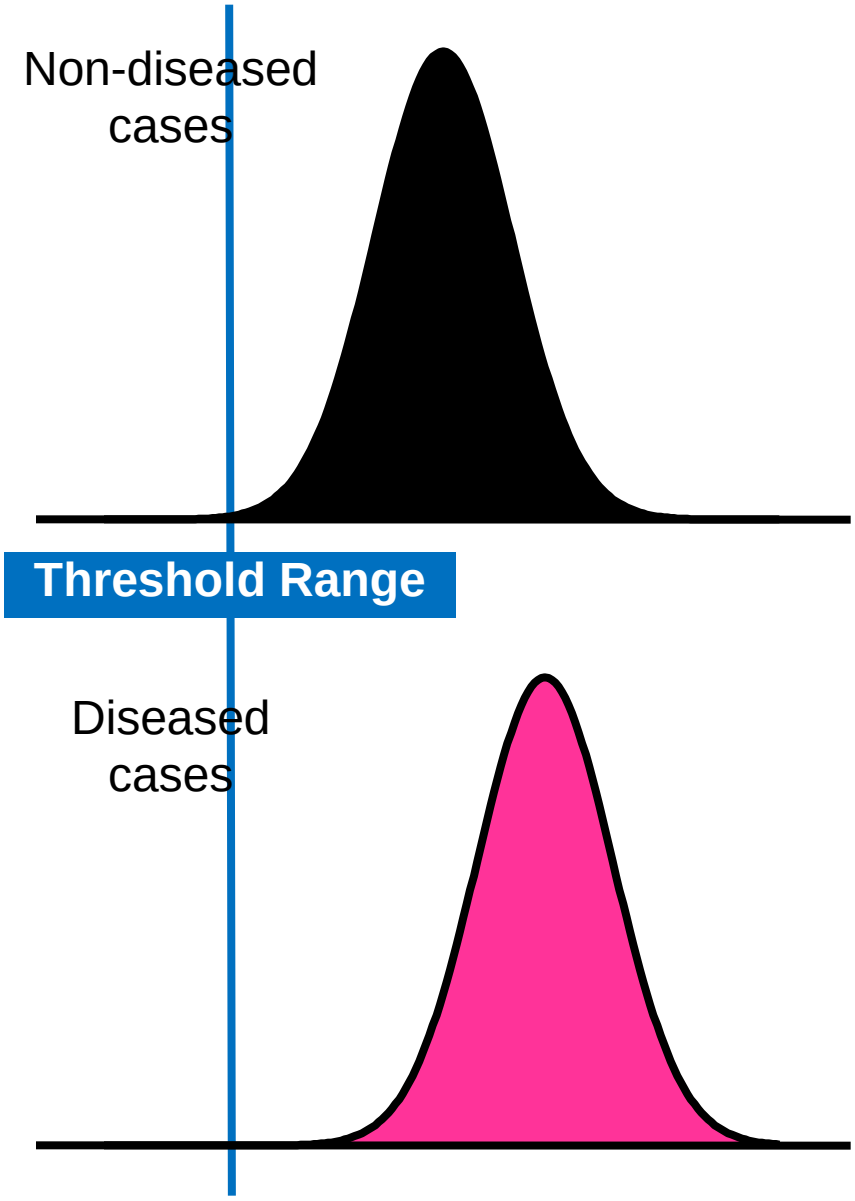
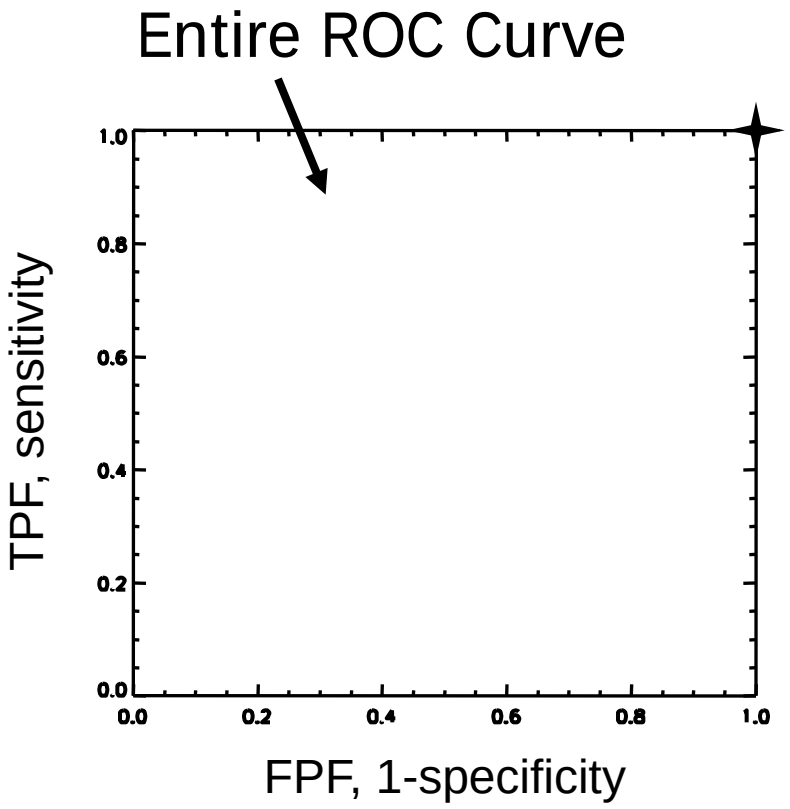
FPF=false negative fraction





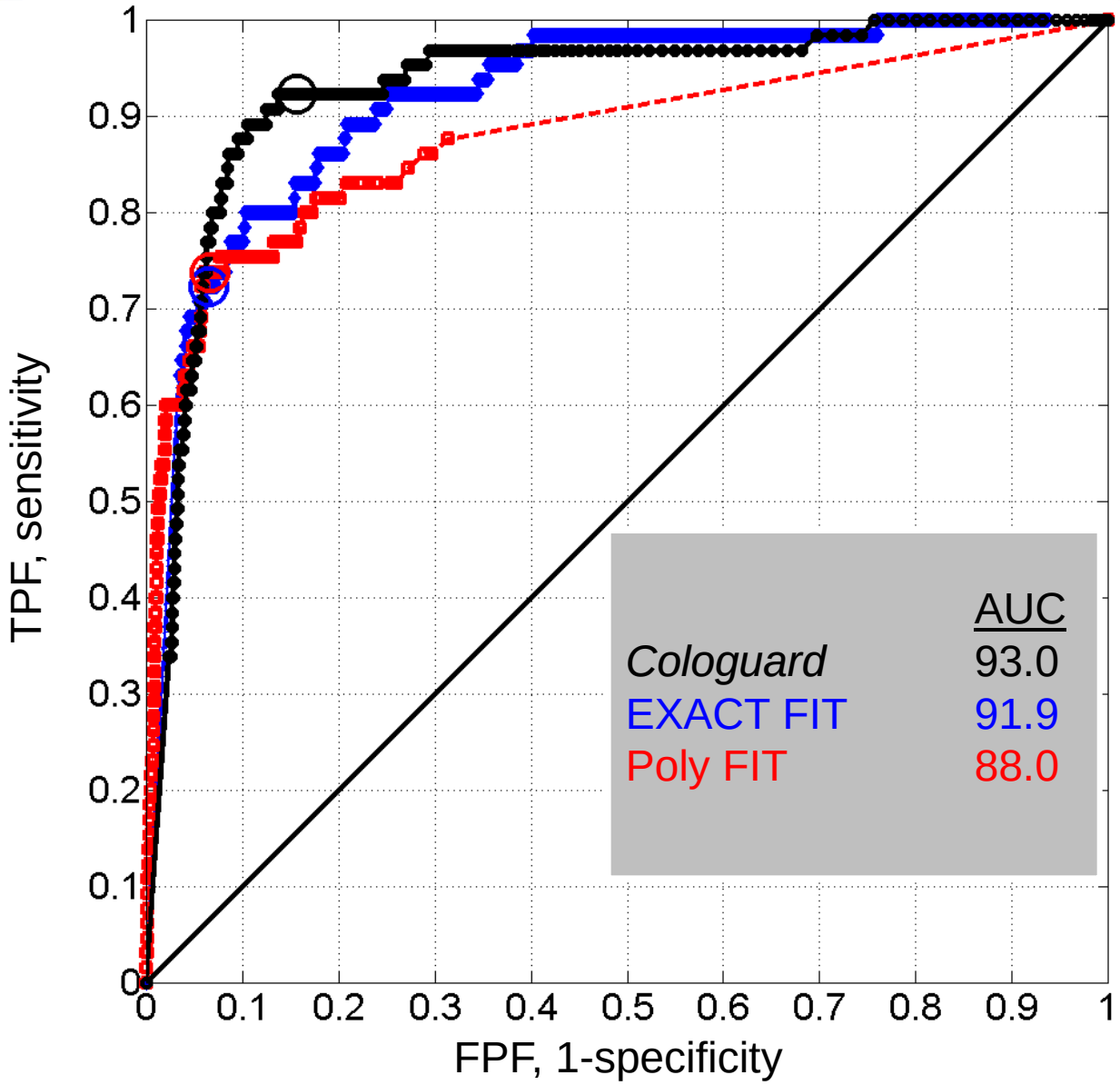
TPF=true positive fraction
FPF=false negative fraction

ROC Analysis: CRC

- Three tests were compared:
  - *Cologuard* composite score
  - PolyMedco FIT (Poly FIT)
  - FIT component of *Cologuard* (EXACT FIT)
- Superimposed on a test's ROC plot is the pair (CRC FPF, CRC TPF) corresponding to threshold
  - 183 for *Cologuard*
  - 101 ng/mL for Poly FIT
  - 204 ng/mL* for EXACT FIT

*for illustrative purposes

CRC

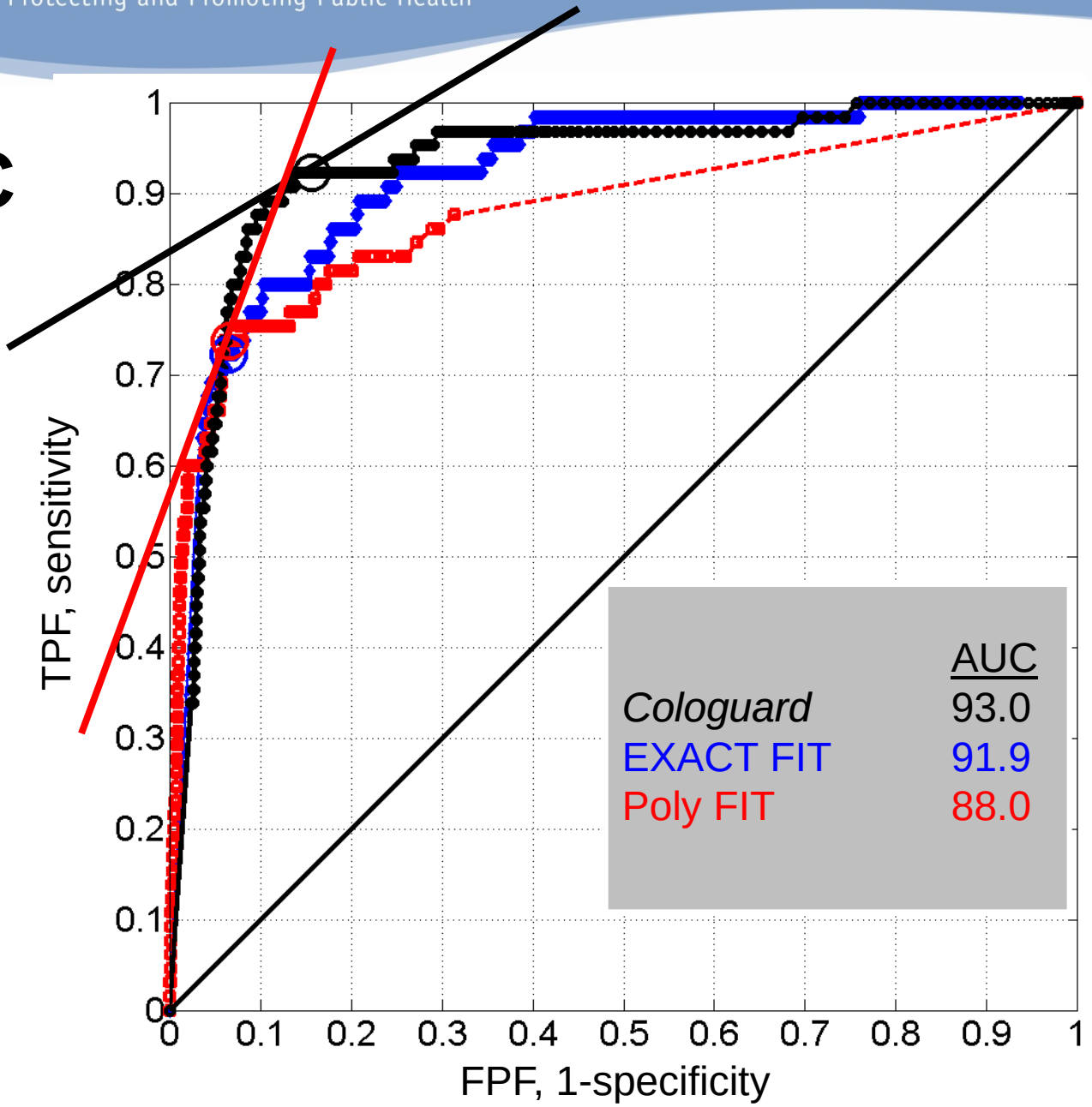

TPF, sensitivity
FPF, 1-specificity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
AUC
Cologuard 93.0
EXACT FIT 91.9
Poly FIT 88.0

AUC (%) under ROC, CRC

Comparison	AUC1	AUC2	Diff	Wald 95% CI	p-value
EXACT FIT – Poly FIT	91.9	88.0	3.9	0.4, 7.5	0.0289
***Cologuard* – Poly FIT**	93.0	88.0	5.0	0.03, 9.9	0.0485
***Cologuard* – EXACT FIT**	93.0	91.9	1.1	-2.4, 4.5	0.5507

- **For CRC AUC,**
  - EXACT FIT was significantly > than Poly FIT
  - *Cologuard* was significantly > than Poly FIT
  - *Cologuard* was not significantly > than EXACT FIT

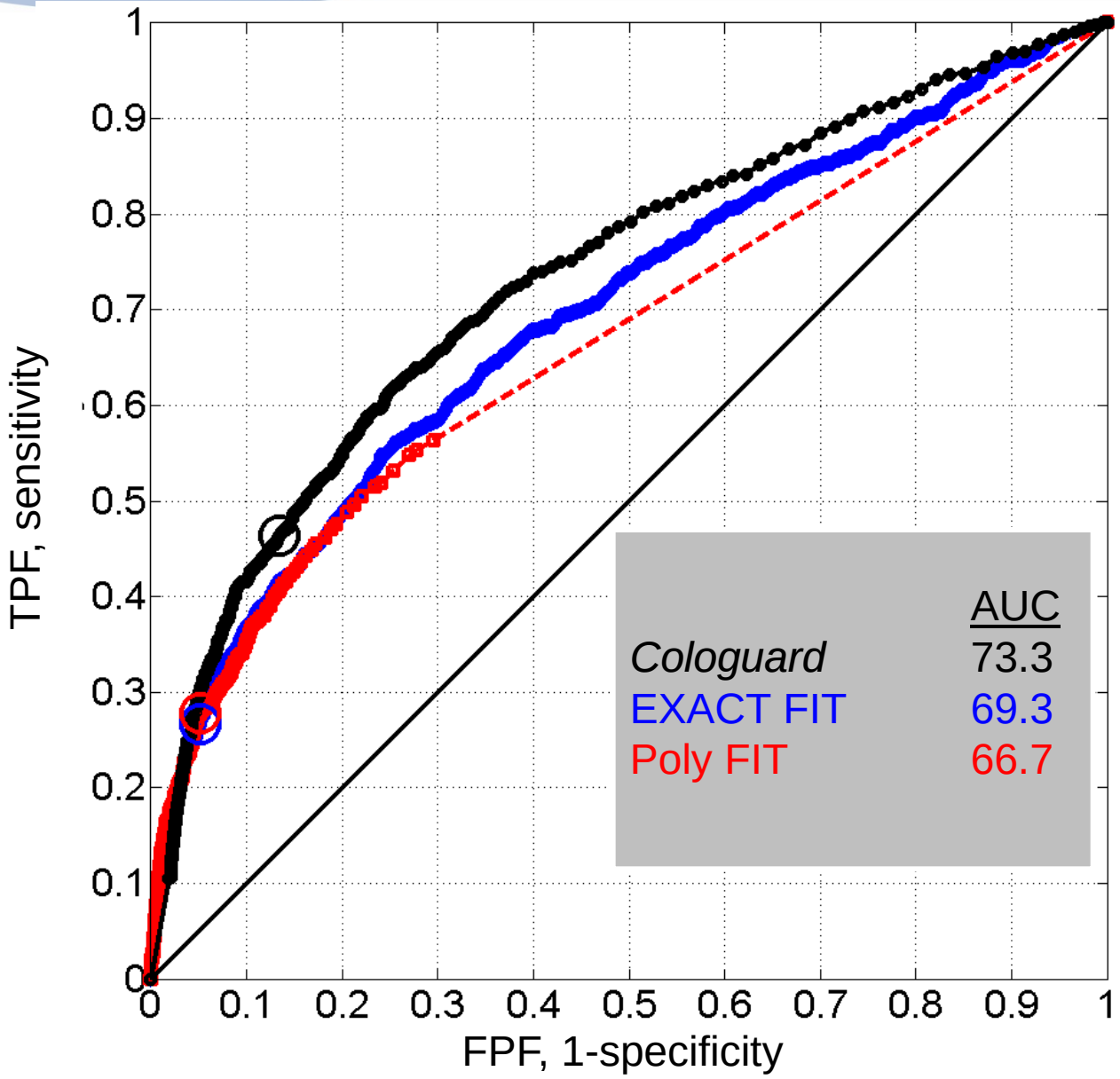
CRC


TPF, sensitivity
FPF, 1-specificity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
AUC
Cologuard 93.0
EXACT FIT 91.9
Poly FIT 88.0

ROC Analysis, AN

Secondary Effectiveness Population

AN


TPF, sensitivity
FPF, 1-specificity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
AUC
Cologuard 73.3
EXACT FIT 69.3
Poly FIT 66.7

AUC (%) under ROC, AN

Comparison	AUC1	AUC2	Diff	Wald 95% CI	p-value
EXACT FIT – Poly FIT	69.3	66.7	2.6	0.9, 4.2	0.0020
***Cologuard* – Poly FIT**	73.3	66.7	6.5	4.4, 8.7	<0.0001
***Cologuard* – EXACT FIT**	73.3	69.3	4.0	1.9, 6.0	0.0002

- **For AN AUC,**
  - EXACT FIT was significantly > than Poly FIT
  - *Cologuard* was significantly > than Poly FIT
  - *Cologuard* was significantly > than EXACT FIT

Benefit-Risk, CRC (FDA)

Secondary Effectiveness Population

Expected Diagnostic Yield in a Hypothetical Screening Population

Hypothetical screening of 100,000 subjects

Assumptions:

Histological Type	Prevalence (n=10840)	*CG* positive fraction (n=9989)	Poly FIT positive fraction (n=9989)
CRC	0.70% (76/10840)	92.31% (60/65)	73.85% (48/65)
AA	7.58% (822/10840)	42.40% (321/ 757)	23.78% (180/ 757)
Cat. 3-6	91.72% (9942/10840)	13.43% (1231/9167)	5.15% (472/9167)

Expected Diagnostic Yield in a Screening Population, CRC

Histological Type	E(N)	*CG* +	FIT +
CRC	700	647	518
Non-CRC	99300	15529	6524
FPs per TP		24.0	12.6

Expected Diagnostic Yield in a Screening Population, CRC

Histological Type	E(N)	*CG* +	FIT +	Difference	Difference ÷ 129
CRC	700	647	518	+129	+1
Non-CRC	99300	15529	6524	+9005	+70
FPs per TP		24.0	12.6		

Safety Evaluation: Colonoscopy AEs†, Non-CRC

Non-CRC	99300	105.6	44.4	+61.2	+0.5

†Assumes risk 0.68% of an adverse event (AE) during colonoscopy (Rutter, CM. 2012)

Benefit-Risk, AN (FDA)

Secondary Effectiveness Population

Expected Diagnostic Yield in a Screening Population, AN

Histological Type	E(N)	*CG* +	FIT +	Difference	Difference ÷ 1542
AN	8280	3863	2321	+1542	+1
Non-AN	91720	12316	4722	+7594	+5
FPs per TP		3.2	2.0		

Safety Evaluation: Colonoscopy AEs†, Cat. 3-6

Non-AN	91720	83.7	32.1	+51.6	+0.03

†Assumes risk 0.68% of an adverse event (AE) during colonoscopy (Rutter, CM. 2012)

Subgroup Analysis*

Primary Effectiveness Population

*Performance goals for subgroup analysis were not pre-specified

Subgroup Analysis, CRC Sensitivity

- Variation by gender **was significant**

  100.0% (34/34) for males
  83.9% (26/31) for females (p=0.021)

- Variation by race **was significant**

  53/55 (96.4%) among Whites

  5/8 (62.5%) among Blacks/African American (p=0.012)

- Variation by age group **was *not* significant**

  100.0% (7/ 7) for age <60 years
  75.0% (3/ 4) for age 60-64 years
  95.0% (19/20) for age 65-69 years
  88.9% (16/18) for age 70-74 years
  100.0% (6/ 6) for age 75-79 years
  90.0% (9/10) for age 80-84 years (p=0.597)

Subgroup Analysis, AA Sensitivity

- Variation by gender **was *not* significant**

  44.7% (201/450) for males
  39.0% (121/310) for females (p=0.1353)

- Variation by race **was *not* significant**

  42.3% (271/641) among Whites
  42.4% (36/ 85) among Blacks/African American (p=0.697)

- Variation by age group **was *not* significant**

  38.0% (65/171) for age <60 years
  42.1% (24/57) for age 60-64 years
  41.5% (125/301) for age 65-69 years
  46.8% (72/154) for age 70-74 years
  46.8% (29/62) for age 75-79 years
  46.7% (7/15) for age 80-84 years (p=0.656, trend p=0.098)

Subgroup Analysis, AN Specificity

- Variation by gender **was significant**
  - 85.8% (3,569/4,161) for males
  - 87.3% (4,398/5,037) for females (p=0.0313)
- Variation by race **was significant**
  - 85.9% (6,639/7,726) among Whites
  - 89.9% (879/ 978) among Blacks/AA (p<0.001)
- Variation by age group **was significant**
  - 92.2% (2491/2703) for age <60 years
  - 89.0% (681/765) for age 60-64 years
  - 85.7% (2871/3352) for age 65-69 years
  - 82.5% (1292/1566) for age 70-74 years
  - 77.8% (480/617) for age 75-79 years
  - 77.9% (152/195) for age 80-84 years (p<0.001)

Subgroup Analysis, Sub-Categories of Category 2, AA

- For adenoma with carcinoma *in situ*/high grade dysplasia (Cat. 2.1), sensitivity was
  - 69.2% for *Cologuard*
  - 46.2% for FIT
- For serrated lesions (Cat. 2.4), sensitivity was
  - 42.4% for *Cologuard*
  - 5.1% for FIT
  - Historically, serrated lesions have been difficult to capture with FIT, as these lesions do not bleed
  - *This subgroup analysis was not pre-specified in the protocol*

Summary of Deep-C Study Results

- **Primary study goals CRC SE ≥ 65%, AN SP ≥ 85%**
  - were met with 1-sided 95% CI lower bound (pre-specified)
  - were also met with 2-sided 95% CI lower bound (FDA)
- If goals are **CRC SE ≥ 65%, CRC SP ≥ 85% (FDA)**
  - for CRC SE, study goal was met
  - for CRC SP, study goal was not met
- After age adjustment to US Census population (FDA)
  - for CRC SE, study goal was met
  - for CRC SP, study goal was met

Summary of Deep-C Study Results

- **Area under the ROC curve (AUC) (FDA)**

CRC

– Difference *CG* – Poly FIT was significantly > 0

– Difference *CG* – EXACT FIT was not significantly > 0

AN

– Difference *CG* – Poly FIT was significantly > 0

– Difference *CG* – EXACT FIT was significantly > 0

FDA Presentation Part III

- Key aspects of clinical studies
- FDA questions for Panel Discussion
- Proposed post approval study
- Additional review and labeling considerations

Review Considerations

- Discussion Question 1 → Test Performance
- Discussion Question 2 → Role of Demographics
  - Screening Guidelines
- Discussion Question 3 → Appropriate Follow-up
  - Screening Practice
  - Dwell Time
- Discussion Question 4 → Appropriate Scope of Claims
- Discussion Question 5 → Longitudinal Study Design

Points for Discussion Question 1

- Study of average risk screening colonoscopy patients
- *Cologuard* (*CG*) compared to FIT
  - lower specificity, higher sensitivity

CG	Specificity	Sensitivity
CRC	84.4	92.3
AN	86.6	46.4
AA		42.4

FIT	Specificity	Sensitivity
CRC	93.4	73.8
AN	94.9	27.7
AA		23.8

- Acceptability of tradeoff
- Potential differences in testing frequency

Points for Discussion Question 2

- Caution for subgroup interpretation
- Considerations for study design and results in relation to demographic factors (age, race and ethnicity, gender)
  - e.g., AN specificity 92.2% for age < 60 years to 77.9% for age 80-84 years
- Study criteria for 50 to 84 years old

➢ Appropriate labeling

Guidelines

- Differences in current CRC screening guidelines
- Process (e.g., IOM standards, ACS revised)
- Content (e.g., USPSTF age)
  - recommends screening in adults beginning at age 50 years and continuing until age 75 years
  - recommends against routine screening for colorectal cancer in adults ages 76 to 85 years
  - recommends against screening for colorectal cancer in adults older than age 85 years
- Upper age limit not specified by ACS, ACG

Screening Practice

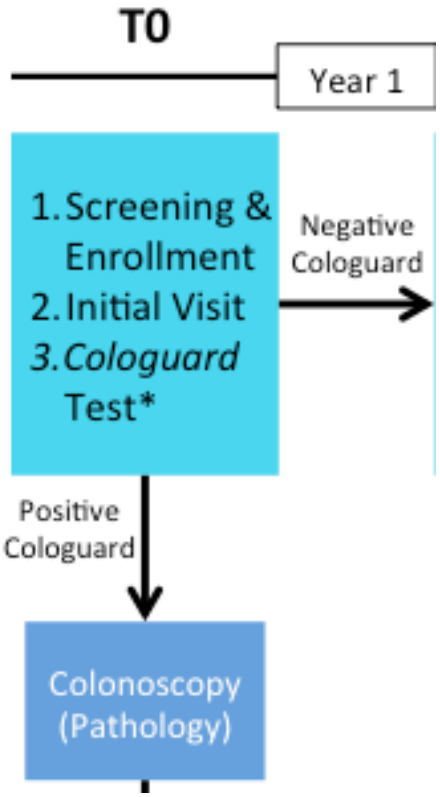
- Deviations from recommendations reported
  - e.g., physicians recommend repeating the FOBT (17.8%) or using other tests (6.6%) instead of diagnostic colonoscopy as follow up for a positive test result

➢ Appropriate IVD materials for patients and physicians

One-Time vs. Repeated

- Test Sensitivity, One-Time Testing, Cross-Sectional Study
- Screening Program Sensitivity, Repeated Testing, Longitudinal Study

➢ Interpret cross-sectional performance accordingly (e.g., consider screening interval)

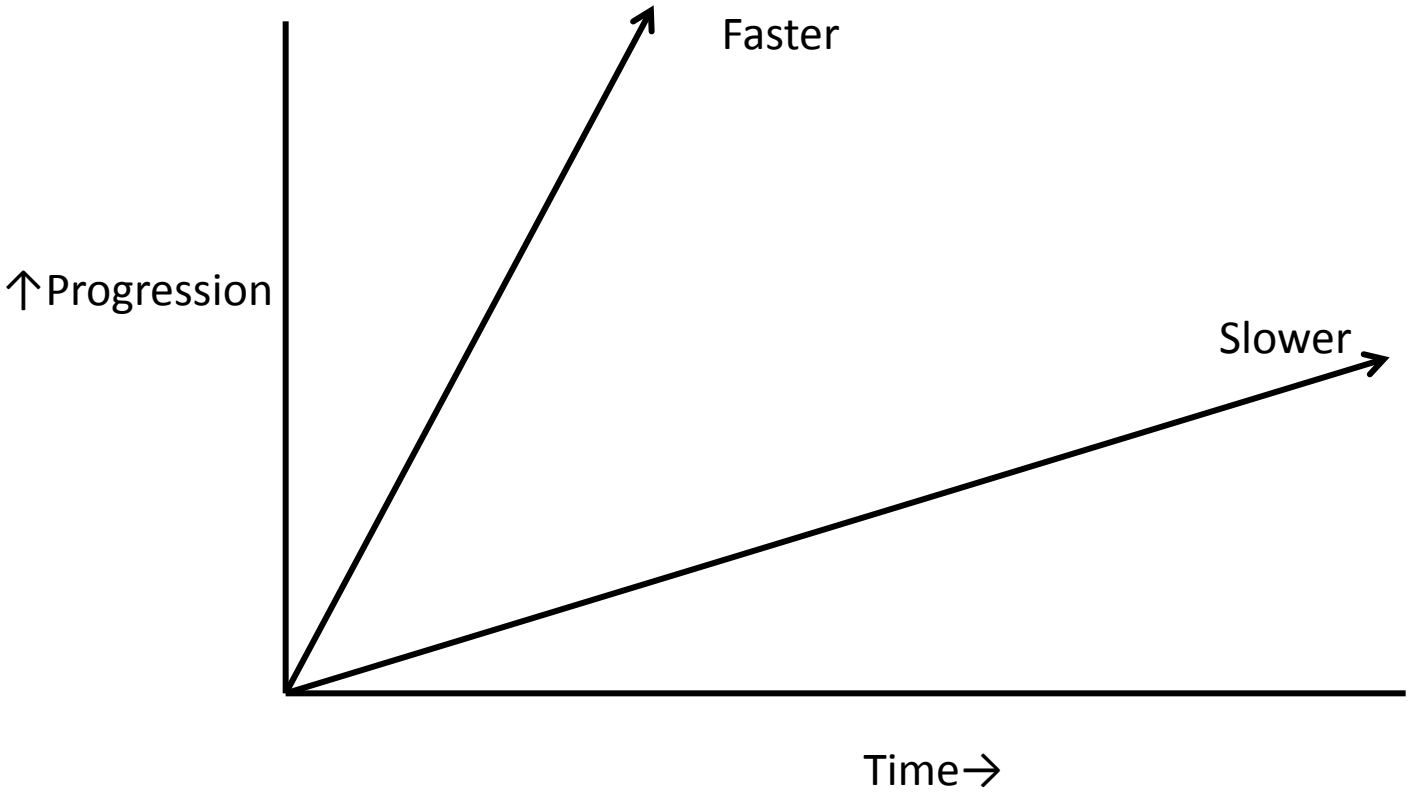


- Cross-sectional study provides performance for initial test
- What happens for patients who initially test negative?
- Performance for additional testing after initially negative test may be evaluated through longitudinal study

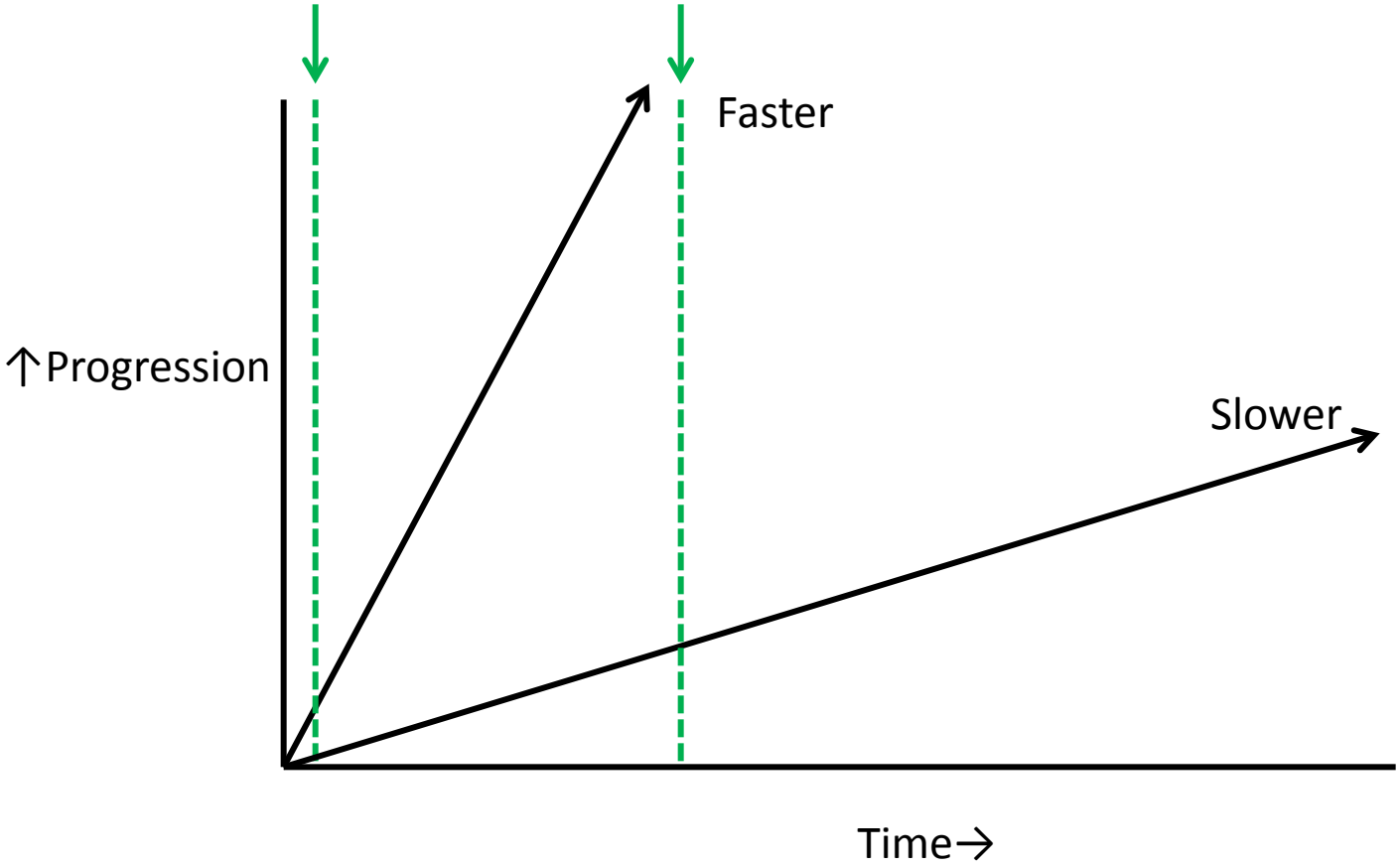
Dwell Times

- Clinically significant lesions
  - Faster growth
  - Slower growth
- Screening program sensitivity
  - More frequent testing with lower sensitivity test
  - Less frequent testing with higher sensitivity test

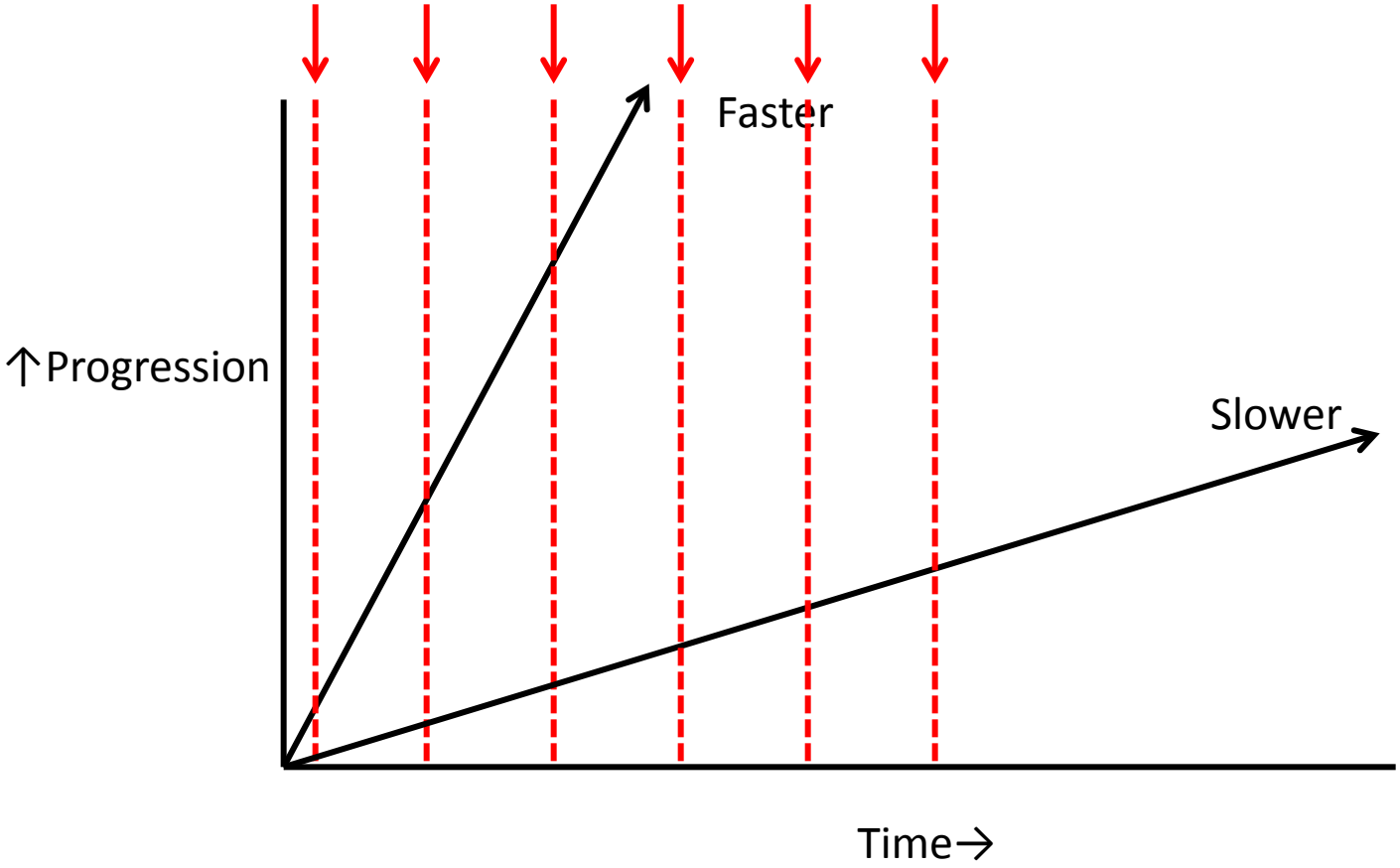
Different Growth Rates



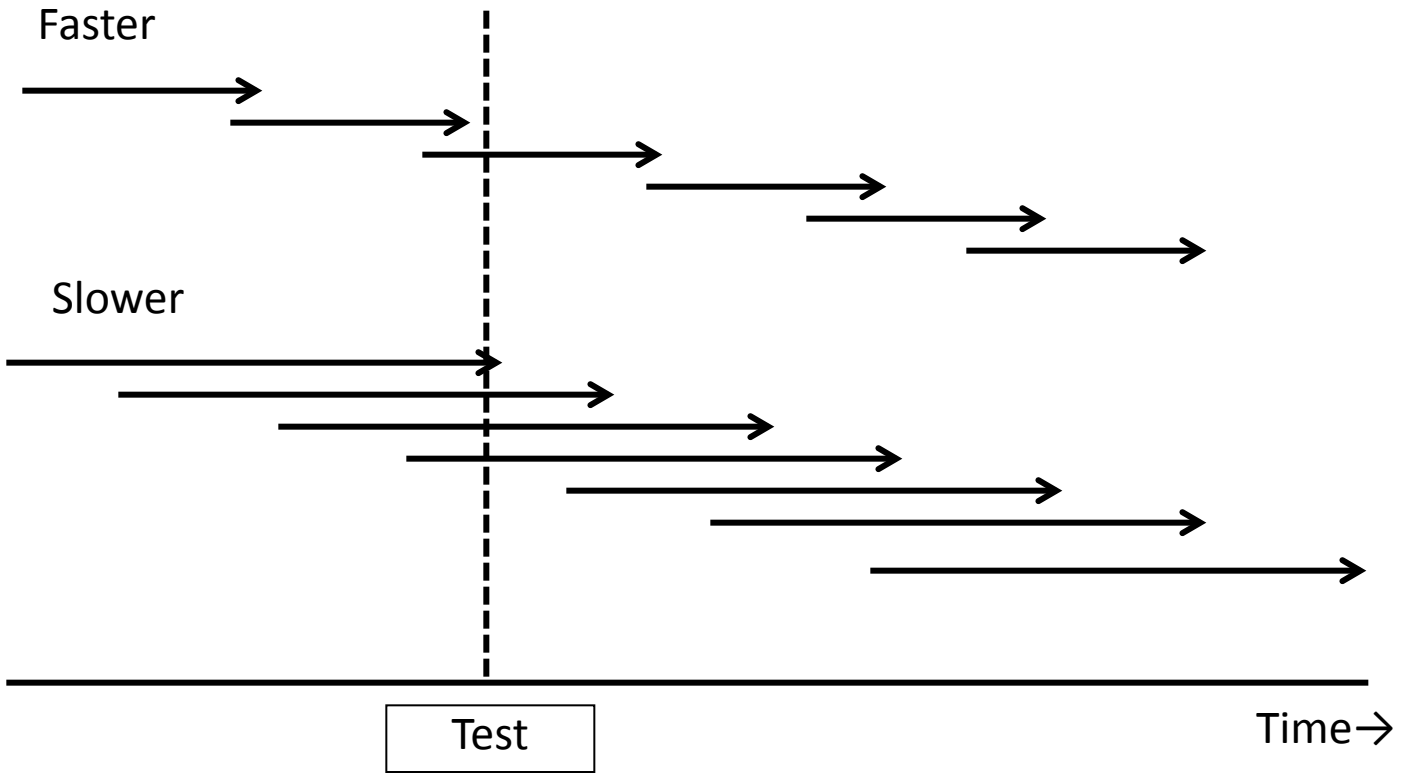
Less Frequent Testing



More Frequent Testing



Dwell Time Distribution



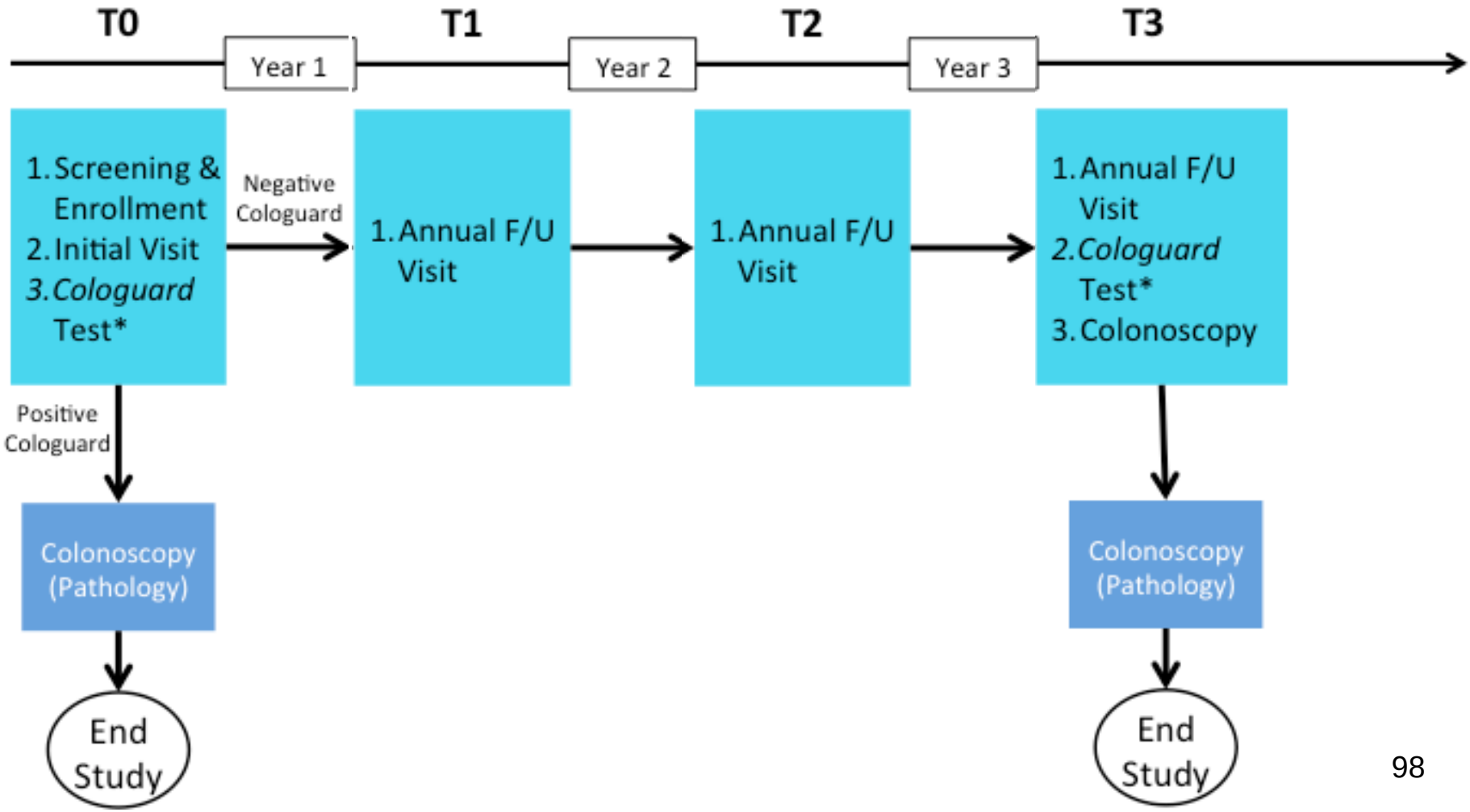
Points for Discussion Question 3

- Follow-up after testing for first time
- Diagnostic colonoscopy if positive
- ➢ Considerations if negative (e.g., time interval, testing method, guidelines, other)
- ➢ Avoid excessive time interval elapsing

Points for Discussion Question 4

- Cross sectional study does not address repeat testing in initially negative patients
- Scope of claims
- Longitudinal study requirement
  - ➢ Negative to positive conversion rate
  - ➢ Diagnostic yield
  - ➢ Predictive values

Sponsor Proposed Study



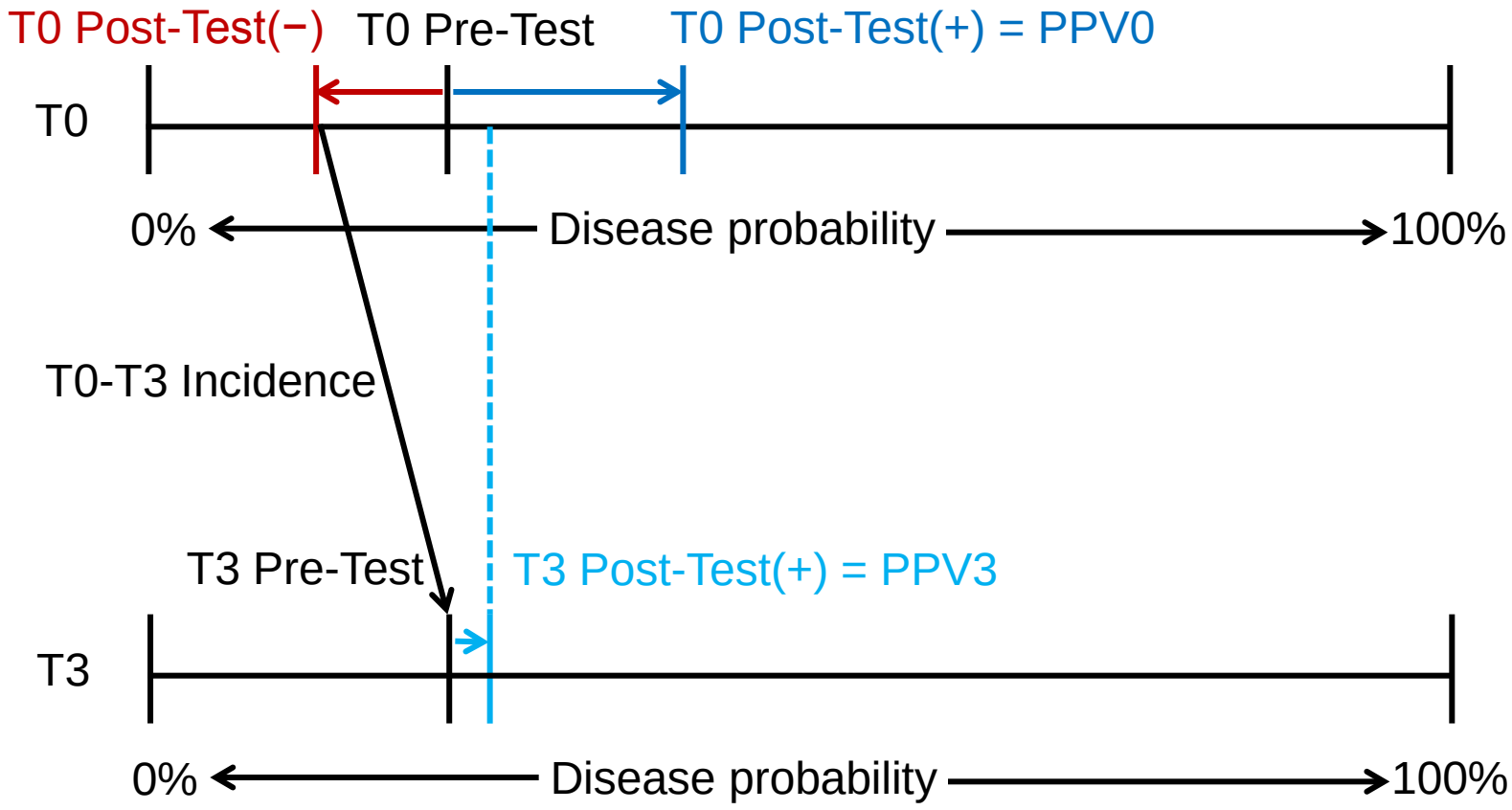
Proposed Study

- Eligibility criteria designed to select patients who are at average risk
- Primary endpoint is risk of CRC/AA among those with a positive Cologuard test at the third year of follow-up (T3) compared to baseline (T0)
- Percentage of patients with CRC/AA at year 3 (T3) is statistically significantly less than at baseline

Points for Discussion Question 5

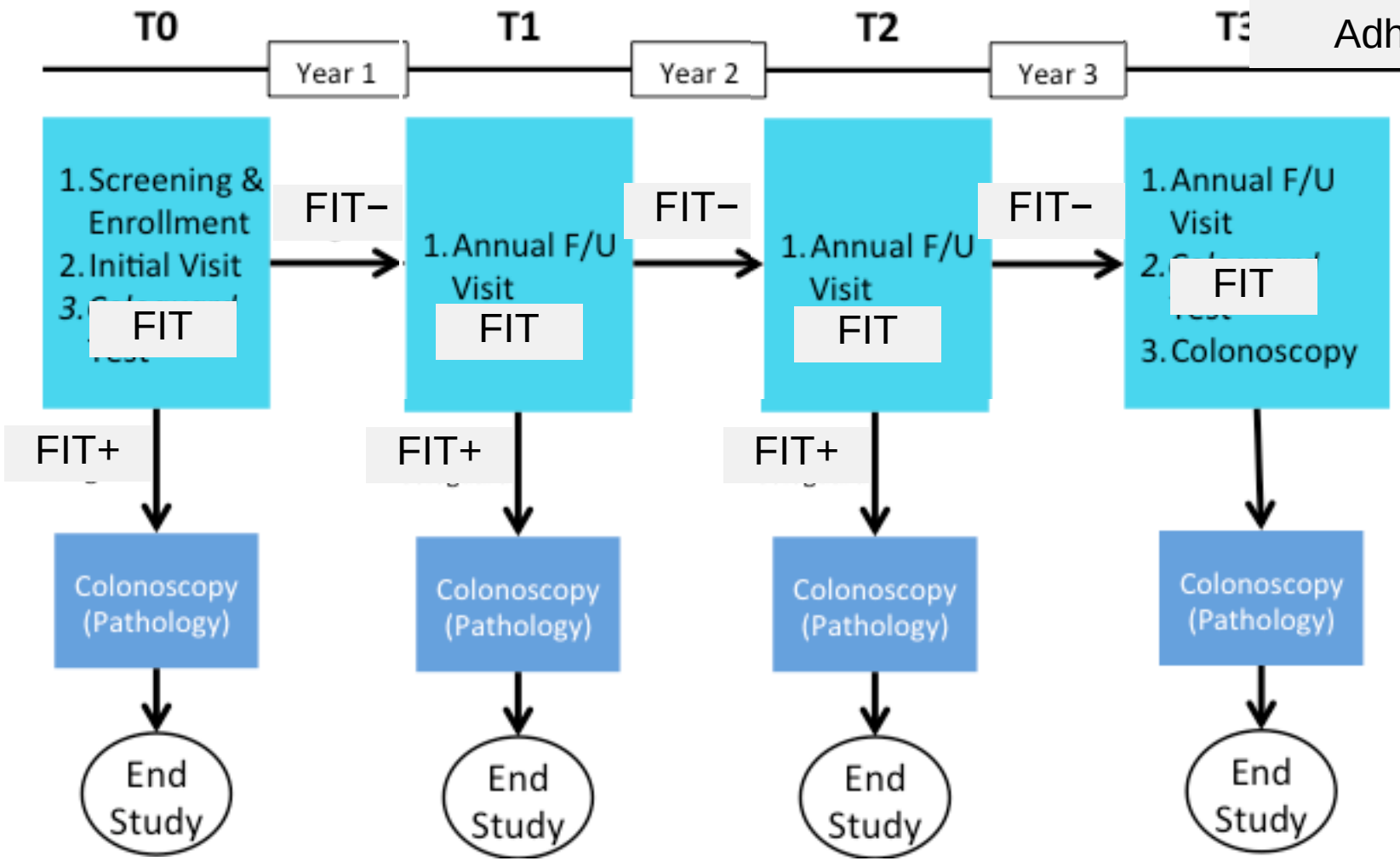
- Study conduct
  - Would forgo other screening options (e.g., annual FIT)
- Statistically and clinically meaningful performance evaluation
  - Comparison to other approaches (e.g., annual FIT)
  - Lower positive predictive value of Cologuard test at T3 could be achieved with limited value from repeat testing

PPV3 < PPV0 ?


T0 Post-Test(−)
T0 Pre-Test
T0 Post-Test(+) = PPV0
T0
0%
Disease probability
100%
T0-T3 Incidence
T3 Pre-Test
T3 Post-Test(+) = PPV3
T3
0%
Disease probability
100%

Annual FIT?

%FIT positive
Diagnostic yield from colonoscopy
Predictive values
Adherence



Summary (Q1 and Q2)

- Discussion Question 1 → Test Performance
  - Tradeoff of lower specificity and higher sensitivity compared to FIT
- Discussion Question 2 → Role of Demographics
  - Screening guideline differences
  - Age range studied
  - Decreased specificity with age

Summary (Q3-Q5)

- Discussion Question 3 → Appropriate Follow-up
  - Screening practice deviations
  - No information on repeating testing including frequency and lesion dwell times
- Discussion Question 4 → Appropriate Scope of Claims
- Discussion Question 5 → Longitudinal Study Design
  - Meaningful performance
  - Comparison to accepted screening option

Thank You

Questions?